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## Visual hallucinations in Parkinson's disease

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## Chapter 4

# Impaired visual processing preceding image recognition in Parkinson's disease with visual hallucinations

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## 4.1 Abstract

**I**MPAIRED visual processing may play a role in the pathophysiology of visual hallucinations in Parkinson's disease. In order to study involved neuronal circuitry, we assessed cerebral activation patterns both before and during recognition of gradually revealed images in Parkinson's disease patients with visual hallucinations, Parkinson's disease patients without visual hallucinations and healthy controls. We hypothesized that, before image recognition, Parkinson's disease with visual hallucinations would show reduced bottom-up visual activation in occipital-temporal areas and increased (pre)frontal activation, reflecting increased top-down demand. Overshoot of the latter has been proposed to play a role in generating visual hallucinations.

Nine non-demented Parkinson's disease patients with visual hallucinations, 14 Parkinson's disease patients without visual hallucinations and 13 healthy controls were scanned on a 3 Tesla MRI scanner. Static images of animals and objects gradually appearing out of random visual noise were used in an event-related design paradigm. Analyses were time-locked on the moment of image recognition, indicated by the subjects' button-press. Subjects were asked to press an additional button on a colour-changing fixation dot, to keep attention and motor action constant and to assess reaction times. Data pre-processing and statistical analysis were performed with SPM5. Bilateral activation of the fusiform- and lingual gyri was seen during image recognition in all groups ( $p < 0.001$ ). Several seconds before image recognition, Parkinson's disease patients with visual hallucinations showed reduced activation of the lateral occipital cortex, compared to both Parkinson's disease patients without visual hallucinations and healthy controls. In addition, reduced activation of extrastriate temporal visual cortices was seen just before image recognition in Parkinson's disease patients with visual hallucinations.

## 4.2 Introduction

PARKINSON'S DISEASE (PD) is a multisystem neurodegenerative disorder, in which deterioration of dopaminergic neurons in the substantia nigra, that project to the striatum, is a classical hallmark (Lang and Lozano, 1998; Braak et al., 2004). Motor symptoms like bradykinesia, rigidity and tremor are dominant characteristics of PD, while non-motor symptoms such as cognitive impairment and visual hallucinations (VH) may additionally occur (Aarsland et al., 2005; Barnes and David, 2001). VH in PD typically consist of complex visual, commonly moving, images lasting for seconds to minutes, experienced in the alert state with eyes open, affecting 30-50 percent of all PD patients (Barnes and David, 2001; Williams and Lees, 2005). Animals, people and objects define the three categories of images that are most frequently seen by hallucinating PD patients. Mostly these VH are non-threatening and the patient maintains insight in the fact that the experiences do not reflect real events (Fenelon et al., 2000; Barnes and David, 2001). Nevertheless, VH may progress to hallucinations with loss of insight or delusions in 80 percent and constitute an important risk factor for nursing home placement (Goetz and Stebbins, 1993). In the present study, we employed fMRI in PD patients with VH (PDwithVH), PD patients without VH (PDnonVH) and healthy control subjects. By assessing functional differences in brain regions implicated in visual perception, we aimed to gain more insight in the origin of VH in PD. In this respect we were particularly interested in visual processing stages preceding actual image recognition.

Hallucinations are defined as involuntary perceptual experiences in the waking state without external visual stimulation (Collerton et al., 2005). Particularly auditory and visual hallucinations are core symptoms in schizophrenia and can be treated with dopamine receptor antagonists. This suggests involvement of the striatum in the pathophysiology of hallucinations. Such association is indeed supported by functional imaging with H<sub>2</sub>O-PET in schizophrenia, showing increased striatum (and cingulate) activation during hallucinations, together with activations in distinct auditory- and visual cortical regions during respectively auditory- and visual hallucinations (Silbersweig et al., 1995). VH may, however, also occur without psychiatric or neurological disease. For example, in Charles Bonnet Syndrome (CBS) complex VH occur secondary to profound visual loss in cognitively normal people (Teunisse et al., 1996). These observations have provided support for the concept that impaired processing of externally presented stimuli may lead to an increased reliance on 'top-down' mechanisms, in which an 'internal generator' may contribute to activations in

appropriate perceptive cortical regions (Silbersweig et al., 1995; Stebbins et al., 2004).

#### 4.2.1 Visual Hallucinations in Parkinson's disease

With regard to VH in PD, a combination of impaired visual processing and attention has been reported (Flowers and Robertson, 1995; Collerton et al., 2005; Meppelink et al., 2008; Diederich et al., 2005). VH in PD have been commonly viewed as an adverse effect of dopaminergic treatment for PD, causing a relative overstimulation of the limbocortical dopaminergic receptors (Bosboom et al., 2004). However, VH in PD may not be associated with the dose or duration of treatment of dopaminergic drugs (Goetz et al., 1998; Holroyd et al., 2001). Moreover, VH have already been reported in the pre-levodopa era (Fenelon et al., 2006). Neuropathologically, VH in PD are associated with increased Lewy body deposition in the temporal lobe (Harding et al., 2002), suggesting that VH in PD are at least partially caused by the disease itself. With fMRI, increased caudate activation has been demonstrated during visual stimulation in PDwithVH, compared to PDnonVH, thus showing some resemblance with the above described functional imaging findings in schizophrenia (Stebbins et al., 2004). This raises the question how the basal ganglia play a role in the generation of hallucinations. The basal ganglia are involved in switching behavior to internal or external sensory stimuli (Redgrave et al., 1999). Their well-structured interconnections with the cerebral cortex by cortico-basal ganglia-thalamo-cortical circuits are organized in parallel loops, which enable the regulation of normal adaptive behavior by selection of motor and non-motor behavioral responses (Redgrave et al., 1999; de Jong and Paans, 2007). Some imaging studies have further shown hyperperfusion of the frontal lobe during VH in PD (Kataoka et al., 2008) and schizophrenia (Silbersweig et al., 1995). Joint activations in the basal ganglia and frontal lobes might thus reflect an aspect of internal image generation in these patient groups. In patients with PD, schizophrenia and CBS increased perfusion or activation of visual association cortices was seen during the occurrence of VH (Kataoka et al., 2008; Silbersweig et al., 1995; Ffytche et al., 1998), while in other studies reduction of either activation, perfusion or metabolism in visual association cortices was seen during rest or simple visual stimulation (Stebbins et al., 2004; Okada et al., 1999; Matsui et al., 2006a; Boecker et al., 2007). In CBS, the latter likely reflects reduced visual cortical processing due to visual deprivation (Ffytche et al., 1998). In PDwithVH, cortical visual processing itself seems to be impaired, as explained below.

### 4.2.2 Impaired visual processing

A wide range of visual perceptual disturbances has been associated with VH in PD, including reduced visual acuity (Matsui et al., 2006b), contrast sensitivity, colour discrimination (Diederich et al., 1998), visual space perception (Ramirez-Ruiz et al., 2007a) and visual object perception (Barnes et al., 2003; Ramirez-Ruiz et al., 2006). Relative hypometabolism of the ventral visual stream in PD patients compared to patients with progressive supranuclear palsy has been proposed to reflect the vulnerability for VH particularly in PD (Klein et al., 2005). Relatively impaired visual processing in PDwithVH could hypothetically lead to compensatory visual processing and internal image generation. In this respect, some resemblance can be seen with the occurrence of VH in CBS, although the cause of underlying visual dysfunction is different. VH in PD tend to occur in dim suboptimal visual circumstances, mostly during the evening (Fenelon et al., 2000). In suboptimal visual circumstances, top-down processes are considered to play an important role in the recognition of objects (Bar et al., 2006). It is thought that a partially analyzed version of the input image is rapidly projected from early visual areas to the prefrontal cortex, where it activates an “initial guess”, which is projected back to the temporal cortex (Bar et al., 2006). There, it is integrated in bottom-up visual processing, in which the visual image is processed from V1 to the occipital-temporal cortex. Several techniques have been used to mimic these suboptimal visual situations, such as backward masking, in which briefly presented images are immediately followed by a masking stimulus, and gradual revelation of objects using panels and visual noise (Bar et al., 2001; James et al., 2000; Grill-Spector et al., 2000). By presenting images that slowly and dynamically appear out of random noise, the speed and content of conscious perception of images can be assessed (James et al., 2000; Reinders et al., 2006; Kleinschmidt et al., 2002; Meppelink et al., 2008). This dynamic presentation of stimuli probably mimics a situation of more natural visual perception. Previous data from our own group has shown that non-demented PDwithVH were slower in recognizing images dynamically popping-out of noise, compared to both PDnonVH and healthy controls (Meppelink et al., 2008).

### 4.2.3 Hypothesis

The aim of the current study was to investigate the distribution of cerebral activations during visual processing in non-demented PDwithVH compared to non-demented PDnonVH and healthy controls. Our hypothesis was that in PDwithVH, impaired bottom-up visual processing induces top-down com-

pensation. During actual hallucinations, this compensation may change into an overshoot of top-down exerted activity, resulting in an increase of activations within a visuo-frontal neuronal network. In the present fMRI study, we did not aim to detect the effect of actual hallucinations, because the included PDwithVH did not perceive them during scanning. The employed paradigm was designed to provoke and identify successive activation patterns during the observation of a display with gradually revealed images. By focusing particularly on activation in the stage preceding image recognition, we aimed to investigate whether the previously found delay in image recognition in PDwithVH (Meppelink et al., 2008) is reflected in changed activations in respectively ventral extrastriate visual cortex, basal ganglia and prefrontal cortex.

## 4.3 Methods

### 4.3.1 Subjects

Thirty-six subjects participated in this study, divided in 3 groups; 9 PD patients who experienced complex VH at least weekly during the last month, 14 PDnonVH and 13 healthy controls. Originally, 12 PD patients with VH and 14 healthy controls were included in this study. Two subjects (one healthy control and one PDwithVH) were excluded because of motion artifacts and two PDwithVH were excluded because they were unable to perform the task as instructed once they were in the scanner. E.g., they pressed the ‘recognition-button’ several times per movie while only one response was requested. PD was diagnosed according to the criteria of the UK PD Society Brain Bank. These three groups were matched for age and level of education. The latter was rated with a Dutch education scale ranging from 1 (elementary school not finished) to 7 (university degree). Both PD groups were also matched for cognition [assessed with the Mini Mental State Examination (MMSE) (Folstein et al., 1975)] and for their level of executive functioning [assessed with the Frontal Assessment Battery (FAB) (Dubois et al., 2000)]. All PD patients were ‘on’ during the assessment. The levodopa-equivalent daily dose (LEDD) was calculated for all patients, according to the formula:  $LEDD = \text{levodopa dose (mg)} + (0.3 * \text{levodopa dose if using entacapone with each dose}) + (\text{slow release levodopa} * 0.7) + (\text{bromocriptine} * 10) + (\text{ropinirole} * 20) + (\text{pergolide} * 100) + (\text{pramipexole} * 100) + (\text{apomorphine} * 10)$  (Esselink et al., 2004). Visual acuity was assessed with the Snellen chart. Demographic and clinical characteristics are described in table 4.1. Exclusion criteria were dementia (MMSE score < 24), neurological disorders other than PD, psychiatric disor-

	PD + VH		PD - VH		HC	
	M (SD)	range	M (SD)	range	M (SD)	range
Age (years)	61.2 (8.2)	45-75	64.6 (7.8)	47-74	58.5 (7.5)	47-71
Education	5.7 (0.7)	5-7	5.7 (0.7)	5-7	5.9 (0.8)	5-7
Disease duration	8.1 (5.0)	2-18	8.7 (4.7)	4-24		
LEDD	855 (543)	240-1970	794 (362)	375-1830		
UPDRS-III	21.4 (7.0)	9-30	20.4 (7.3)	6-30		
MMSE	26.8 (1.0)	25-28	27.4 (1.3)	25-29	27.9 (0.9)	26-29
FAB	15.7 (1.8)	12-17	16.8 (1.5)	13-18	17.4 (1.2)	14-18
Visual acuity* (Snellen)	0.94 (0.1)	0.8-1.0	0.91 (0.1)	0.8-1.0	0.95 (0.1)	0.5-1.0
Males: n (%)	5 (55 %)	11 (79 %)	9 (69 %)			
Females: n (%)	4 (45 %)	3 (21 %)	4 (31 %)			

**Table 4.1:** Demographic and illness characteristics of Parkinson’s disease patients with visual hallucinations (PD+VH; n=9), PDnonVH (PD-VH; n=14) and healthy controls (HC; n=13). \* Corrected with glasses, when necessary.

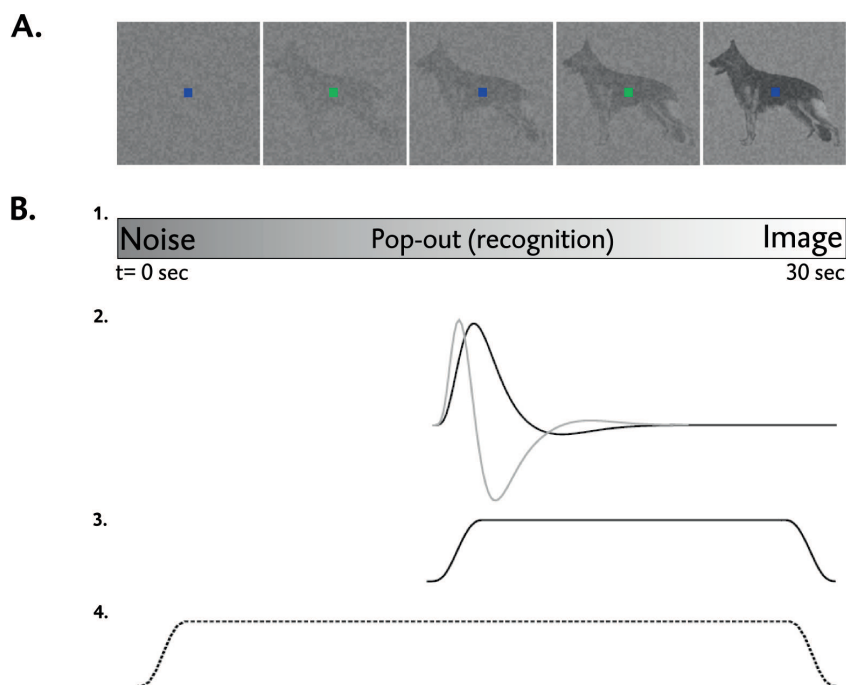
ders, visual acuity less than 50 percent (Snellen chart) and visual field defects. This study was approved by the Medical Ethical Committee of the University Medical Center Groningen. All participants signed an informed consent prior to study inclusion.

### 4.3.2 Clinical tests and statistics

Contrast sensitivity was assessed in all subjects using the Mars contrast sensitivity test (Arditi, 2005). All PD patients were asked to fill in a self-report depression scale [Beck Depression Inventory, BDI (BECK et al., 1961)]. The severity of motor symptoms in PD patients was rated with the Unified PD Rating Scale (UPDRS), part III. Severity of VH in PD patients was assessed with part B “Hallucinations” of the Neuropsychiatric Inventory and a questionnaire based on the characteristics of VH in PD patients as described by Barnes and David (Barnes and David, 2001).

Not all variables were normally distributed in all three groups. Therefore, the non-parametric Mann-Whitney and Kruskal-Wallis tests were used to investigate these non-normally distributed variables. An ANOVA was used to compare normally distributed variables. The three groups were compared concerning their contrast sensitivity and visual acuity using the Kruskal-Wallis test. In addition, the Mann-Whitney test was used to investigate firstly, if PDwithVH differed from PDnonVH and secondly, if PDnonVH differed from healthy controls. Differences in age were investigated using an ANOVA. Scores of PD patients on the BDI, LEDD, MMSE and UPDRS-III were compared using the Mann-Whitney test.





**Figure 4.1: fMRI paradigm and design.** (A) Image of a dog, gradually appearing out of noise. Subjects pressed a button when the image was recognized. An additional button press was required on an infrequently colour changing fixation square, to keep attention constant and to assess reaction times. (B) fMRI design; 1. Image recognition movies start with 100 random white noise at  $t=0$  sec. Images gradually appear, with the pop-out (recognition) being between 0 and 30 seconds; 2. Hemodynamic Response following the pop-out; 3. Visual percept of the image; 4. Block of 30 seconds, representing motor response on the colour change and visual input.

### 4.3.3 fMRI paradigm and experimental procedure

A total of 50 pictures of animals (22), well-known objects (22) and meaningless objects (6, control) were used to create a paradigm in which pictures gradually pop out of random uniform visual white noise (figure 4.1A). Movie stimuli were generated in Matlab 5 on an Apple Macintosh computer running Mac OS 9.2.1 using some of the routines of the Psychtoolbox (Brainard, 1997; Pelli, 1997). Movies were created from gray scale pictures that were first normalized to have their mean luminance equal to the background level. Noise contrast remained constant throughout the duration of the 30-second movie. Image contrast (and thus signal-to-noise) increased linearly over time causing the image to gradually appear out of the noise. Perceptual recognition (“pop-out”) occurred from 10 to 28 seconds after initial movie onset. All movies were created from grey-scale pictures with a resolution of 300 by 300 pixels. Movies were shown at twice this size (600x600 pixels). The movies were presented using the “Presentation” program (Neuro Behavioral Systems, Inc. CA, USA). They were projected by a beamer (resolution 1024 x 768 pixels, Barco, Belgium) on a screen (display dimensions 44 x 34 cm), viewed by the subject via a mirror placed at a distance of 11 cm from the face. The distance between the mirror and the screen was 64 cm and the stimuli covered approximately 18 degrees of the visual field. If necessary, visual acuity of the subject was corrected using MRI-compatible lenses.

During presentation of the movie, a central fixation square changed colour with random intervals. Subjects had to report such change (to keep attention constant) by pressing a button with their right middle finger on an MR compatible response-box (fORP, Current designs, Inc. U.S.A.). Per subject, the mean reaction time of the response to the colour change was calculated. Subjects were further instructed to press a button with their right index finger at the moment that they recognized the object or animal, i.e. at the moment of the perceptual pop-out. Before each session, this paradigm was practiced outside the scanner, while verbal responses were used to verify recognition of the images. In this way, we assessed whether subjects understood the task correctly and whether they indeed recognized the images. The mean reaction time on the colour change was subtracted from the image recognition times. Movie stimuli were presented in two runs, 25 per run. In between the two runs, an anatomical, T1 weighed scan was acquired.

### 4.3.4 MRI characteristics

Data acquisition was performed using a 3 T Philips MR system (Best, The Netherlands) with a standard 6 channel SENSE head coil. Functional images were acquired with a gradient echo, i.e. echo planar imaging, T2\* Blood Oxygen Dependent Level (BOLD) contrast technique in an ascending order with a TE of 35 ms, a TR of 2.3 seconds, 35 slices per TR, 450 volumes per run, isotropic voxels 3 x 3 x 3 mm and an axial orientation.

A T1 weighted 3D anatomical scan was acquired to obtain high resolution anatomical information, isotropic voxels 1 x 1 x 1 mm, matrix size = 256 x 256 and an axial orientation.

### 4.3.5 Psychophysics

The mean reaction time on the colour change of the fixation square was calculated per subject and averaged over groups. Reaction times were not normally distributed; differences between groups were investigated using the non-parametric Kruskal-Wallis test. The Mann-Whitney test was used to investigate between which groups differences exist (PDwithVH versus PDnonVH, PDwithVH versus healthy controls, PDnonVH versus healthy controls).

The mean image recognition time over all movies was calculated per subject and averaged over groups. The percentage of unrecognized images was calculated per subject and averaged over groups as well. Unrecognized movies were considered as missing values. Mean image recognition times were normally distributed, differences between groups were investigated using ANOVA. A Helmert contrast was used to determine firstly, if healthy controls differed significantly from both PDnonVH and PDwithVH and secondly, if PDnonVH differed from PDwithVH.

### 4.3.6 fMRI data analysis

Image processing and statistical analysis were conducted with Statistical Parametric Mapping (SPM, Friston et al. (1995)) version 5 (2005, Wellcome Department of Cognitive Neurology, London, UK; [http : //www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Pre-processing included slice time correction, realignment, coregistration of functional and anatomical scans and spatial normalization (to the template of the Montreal Neurological Institute, MNI). Images were smoothed using a Gaussian filter of 8 mm FWHM. Analyses were time-locked on the perceptual pop-out in an event-related design. In addition to the hemodynamic response

function (HRF), temporal and dispersion derivatives were modeled as well (Friston et al., 1998). Apart from the pop-out, a 30 seconds block of visual input and motor response as well as a block of the visual percept, lasting from the pop-out until the end of the movie, were modeled (figure 4.1B). Movement parameters were included as covariates. T-contrasts of the pop-out with respect to baseline (passive viewing of a fixation cross, projected on a dark background) were made for each subject. A Finite Impulse Response (FIR) analysis was used to investigate temporal dynamics. Again analyses were time-locked to the pop-out (minus 3TR). Basis functions (FIR) were generated using the following settings: duration 3.5TR, order 7. Thus, mean whole brain activations in seven time bins of 0.5 TR (=1.15 seconds) each, were assessed from 3TR (=6.9 seconds) before pop-out until 0.5TR (=1.15 seconds) after the pop-out. On a 2nd level (random effect analysis), the T-contrasts of the pop-out were analyzed per group, using an ANOVA (flexible factorial). The ANOVA was also used to make comparisons between PDwithVH, PDnonVH and healthy controls. FIR data on a 2nd level were also analyzed using an ANOVA (flexible factorial), to assess temporal dynamics on a group level and to make group comparisons. FIR results for the six time bins before pop-out, the seventh bin being non-informative due to excess activation at the given threshold, were rendered on 3D standard MNI brains.

Regions of interest (ROIs) were defined based on the FIR group comparisons that showed significant activation differences in PDwithVH, compared to PDnonVH and healthy controls. Time courses of activation in these ROIs were plotted for all three groups.

## 4.4 Results

### 4.4.1 Characteristics subjects

The three groups were matched for age (ANOVA:  $F=2.13$ ,  $p=0.13$ ) and level of education (Kruskal-Wallis Test:  $\chi^2=0.82$ ,  $p=0.70$ ). PD groups were matched for cognition (MMSE;  $z=-1.09$ ,  $p=0.27$ ) and executive functioning (FAB;  $z=-1.77$ ,  $p=0.08$ ). In the group of 9 PDwithVH, 1 reported having VH about once a week, 6 had VH several times per week and 2 reported having VH several times a day. Thirty-three percent of the hallucinating PD patients reported that they became upset during their VH and 44 percent considered their VH as a moderate to severe emotional burden. Forty-four percent experienced VH of people and animals, 33 percent of only people, 11 percent of only animals and 11 percent of animals and objects. None of the PDwithVH experienced VH

during the testing. Neither did they report a relationship between their VH and the intake of dopaminergic medication. LEDD scores were also not significantly different in PDwithVH, compared to PDnonVH ( $t=0.33$ ,  $p=0.74$ ). Two subjects (PDwithVH) used clozapine for their VH, while none of the subjects used cholinesterase-inhibitors or anti-cholinergics. Of PDwithVH, 2 patients also experienced visual illusions and 2 other patients from this group occasionally experienced “presence of a person” hallucinations. With regard to visual abilities, the Kruskal-Wallis showed a significant difference on contrast sensitivity ( $\chi^2=9.19$ ,  $p=0.01$ ) between the three groups. Healthy controls had significantly higher contrast sensitivity compared to both PDnonVH ( $z=-2.88$ ,  $p=0.004$ ) and PDwithVH ( $z=-2.14$ ,  $p=0.032$ ), while no significant differences were found between the two PD patients groups ( $z=-0.20$ ,  $p=0.84$ ). Visual acuity was equal in all three groups (Kruskal-Wallis:  $\chi^2=1.83$ ,  $p=0.40$ ).

#### **4.4.2 Task performance**

All subjects were able to perform the task adequately. Mean reaction time on the colour change of the fixation square (standard deviation) was 761 (150) ms for PDwithVH, 814 (337) ms for PDnonVH and 575 (126) ms for healthy controls. The Kruskal-Wallis test showed significant differences between groups ( $\chi^2=11$ ,  $p=0.004$ ). The Mann-Whitney showed no significant difference between PDwithVH and PDnonVH ( $z=-0.25$ ,  $p=0.80$ ), while both PDwithVH and PDnonVH were significantly slower, compared to healthy controls ( $z=-2.6$ ,  $p=0.009$  and  $z=-3.0$ ,  $p=0.003$ , respectively). Some pop-out movies were more difficult than others, leading to delayed recognition of the image. The mean percentage of images that were recognized in healthy controls was 96 percent, whereas the mean percentage of recognized images was 86 percent in PDnonVH and only 76 percent in PDwithVH. Mean image recognition time (standard deviation) over all movies was 17.41 (1.82) sec in the healthy controls, 20.18 (2.18) sec in PDnonVH and 20.19 (2.23) sec in PDwithVH. The ANOVA showed significant differences between groups for the mean image recognition time ( $F=7.58$ ,  $p=0.002$ ). The Helmert contrast showed that healthy controls were significantly faster than PDnonVH and PDwithVH ( $p=0.001$ ), while PDwithVH and PDnonVH had the same mean image recognition time ( $p=0.98$ ).

### 4.4.3 Activation at the moment of pop-out

At the moment of pop-out, robust bilateral activations were seen in the fusiform gyrus and lingual gyrus in all groups ( $p < 0.001$ , corrected, see figure 4.2 and table 4.2A). When groups were compared, no differences were observed.

### 4.4.4 Activation before pop-out, within group analysis

The dynamic presentation in which images gradually appeared was associated with the temporal evolution of a changing pattern of cerebral activations that was different for each of the three groups (figure 4.3A). In the healthy controls, the fusiform gyrus was already activated before pop-out ( $p < 0.001$ , corrected at  $-1.2 \rightarrow \text{pop-out}$ ).

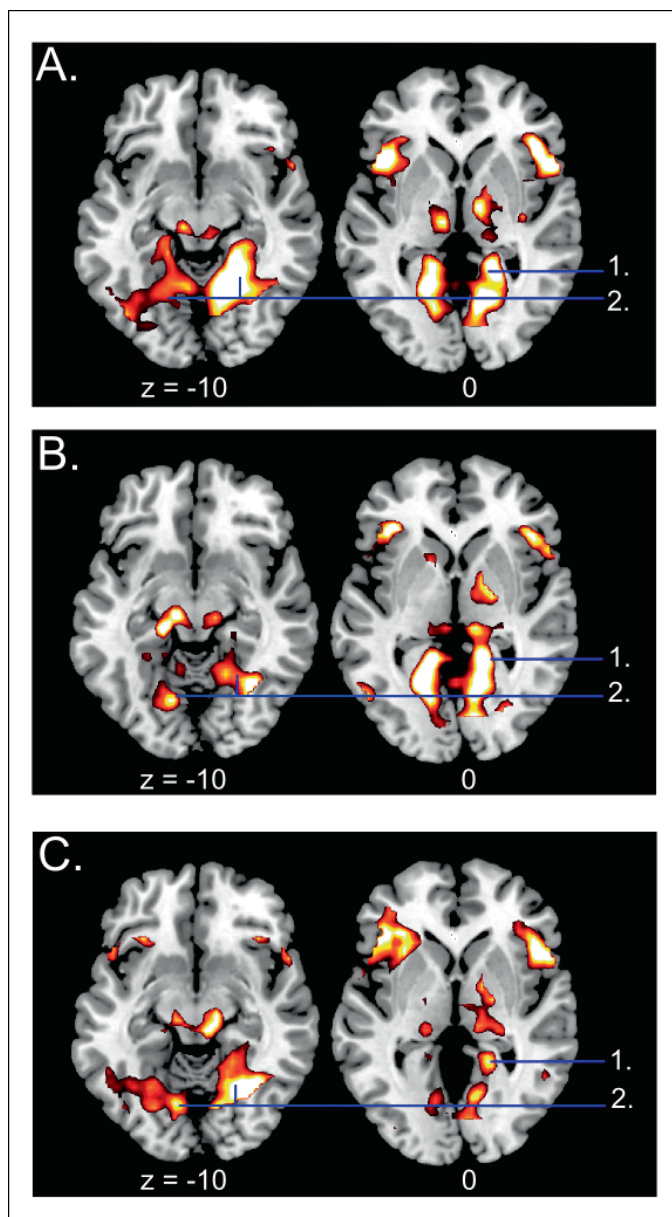
PDnonVH did not show significant activation of the fusiform gyrus before pop-out, but showed activation of the middle occipital cortex and the inferior frontal gyrus at this stage ( $p < 0.001$ , corrected and  $p < 0.001$ , uncorrected, respectively).

PDwithVH did not show significant activation of the fusiform gyrus before pop-out either, but showed activation of the parietal cortex bilaterally. At a lower threshold ( $p < 0.05$ ), the occipital and frontal cortices were activated as well in PDwithVH (data not shown).

### 4.4.5 Activation before pop-out, group differences

*PDwithVH, compared to PDnonVH and healthy controls*

PDwithVH showed a significant reduction of cortical activation, compared to both PDnonVH and healthy controls, while no increases were seen in PDwithVH when compared to the other two groups. The decrease of activation in PDwithVH was already seen several seconds before pop-out. All changes in activation before pop-out at  $p < 0.001$  (cluster-level, uncorrected for the entire brain volume) are reported (table 4.2B and C). After volume correction, corrected statistical significance concerning these effects are partly influenced by the summed size of confluent clusters. At  $-5.8 \text{ sec} \rightarrow -4.6 \text{ sec}$  PDwithVH showed significantly decreased activation of bilateral occipital cortex compared to both PDnonVH ( $p < 0.001$ , uncorrected) and healthy controls ( $p < 0.001$ , corrected). In addition, PDwithVH showed significantly decreased activation of the left inferior parietal cortex, compared to healthy controls ( $p < 0.001$ , uncorrected, see figure 4.3B and table 4.2B and C). At  $-3.5 \text{ sec} \rightarrow -2.3 \text{ sec}$  PDwithVH showed decreased activation of the superior frontal gyrus,



**Figure 4.2: Activation during image recognition.** Activation of the fusiform gyrus (1) and lingual gyrus (2) during image recognition in healthy controls (A), PDnonVH (B) and PDwithVH (C).

compared to PDnonVH ( $p < 0.001$ , corrected), while a trend towards decreased activation in this region was seen in PDwithVH when compared to healthy controls (data not shown). At  $-1.2 \text{ sec} \rightarrow \text{pop-out}$ , PDwithVH showed significantly decreased activation of the fusiform gyrus bilaterally and the left lingual gyrus, compared to both PDnonVH and healthy controls ( $p < 0.001$ , corrected). In addition, PDwithVH showed decreased activation of the cingulate cortex and the right middle frontal gyrus, compared to both PDnonVH and healthy controls ( $p < 0.001$ , uncorrected and corrected, respectively).

No increased activations in PDwithVH were observed, compared to either PDnonVH or healthy controls. Time courses of pre-pop-out effects the left fusiform gyrus, which were similar to that of the right fusiform gyrus, the inferior- and middle frontal gyri, are plotted in figure 3.4.

## 4.5 Discussion

The paradigm applied in this fMRI study was designed to identify activation changes in circuitry particularly related to visual processing preceding image recognition. With the visual task involving the gradual revelation of complex images (animals and objects), we demonstrated that PDwithVH, compared to PDnonVH and healthy controls, had similar activation patterns at the moment of image recognition, but that marked differences occurred in the stage preceding image recognition. This underscored the importance to apply the dynamic paradigm with gradually revealed images, instead of clear static images.

### 4.5.1 Visual object processing

The moment of pop-out, i.e. the moment at which the images of animals and objects were recognized after gradually appearing out of random noise, was related to marked activation in appropriate secondary visual regions such as the fusiform and lingual gyri in all groups. This provided support for the robustness of our paradigm.

The mean time it took to recognize the image was similar in PDwithVH and PDnonVH, while both groups were significantly slower in recognizing the images than healthy controls. Because PDwithVH recognized only 76 percent of the images, compared to 86 percent in PDnonVH, these results are probably an underestimation. When images were not recognized in 30 seconds, a missing value was reported. If image recognition movies would have lasted



## A. Activation at the moment of pop-out

Contrast:	Anatomical region	MNI-coordinates	T (voxel level)	p-value (cluster level)
HC	fusiform R	30,-36,-21	9.08	<0.001, corrected
	fusiform L	-39,-69,-15	5.34	<0.001, corrected
	lingual R	18,-42,0	6.01	<0.001, corrected
	lingual L	-21,-54,0	6.40	<0.001, corrected
PD	fusiform R	30,-57,-15	6.25	<0.001, corrected
	fusiform L	-35,-43,-15	4.76	<0.001, corrected
	lingual R	15,-45,3	8.14	<0.001, corrected
	lingual L	-18,-57,3	7.47	<0.001, corrected
VH	fusiform R	30,-36,-21	7.52	<0.001, corrected
	fusiform L	-31,-73,-16	4.40	<0.001, corrected
	lingual R	18,-45,3	6.01	<0.001, corrected
	lingual L	-12,-69,-6	6.19	<0.001, corrected

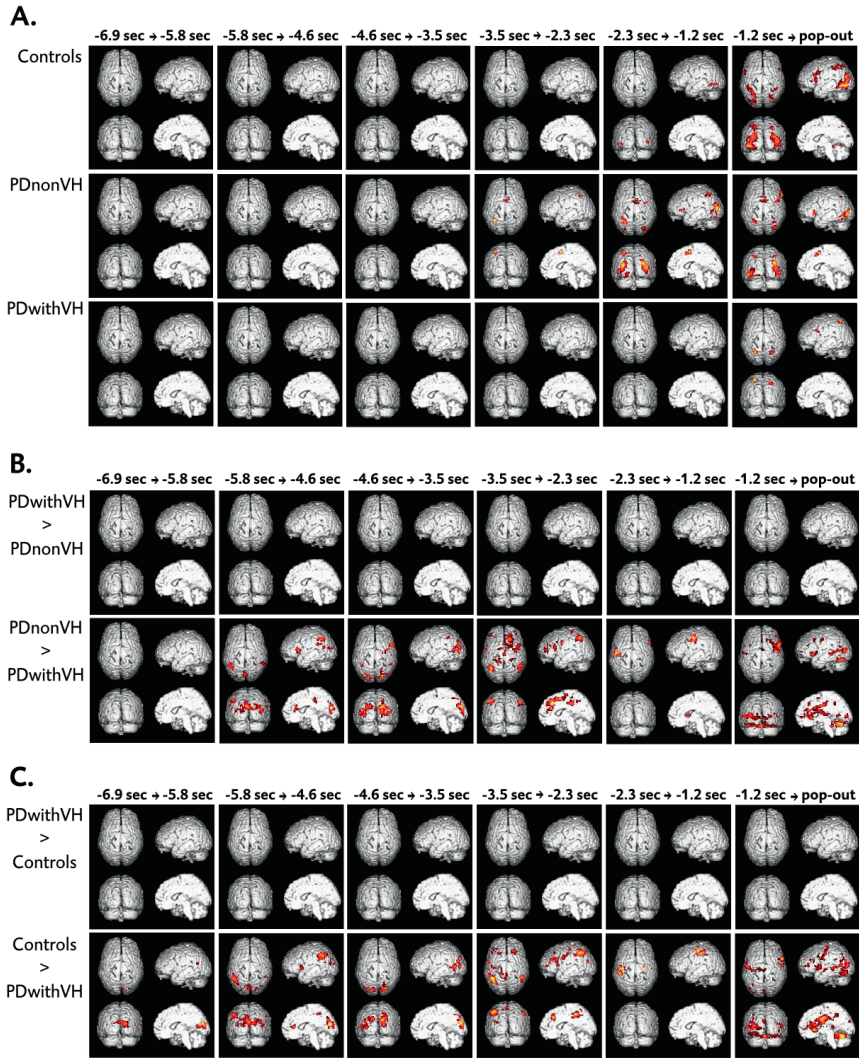
## B. Before pop-out: PDnonVH versus PDwithVH

Contrast:	Anatomical region	MNI-coordinates	T (voxel level)	p-value (cluster level)
PD2 - VH2	calcarine L	-3, -81, 18	2.62	<0.001, uncorrected
	occipital sup. R	18, -84, 18	2.41	<0.001, uncorrected
PD3 - VH3	occipital sup. R	24, -75, 30	3.08	<0.001, uncorrected
	occipital mid. R	42,-81,12	2.62	<0.001, uncorrected
PD4 - VH4	frontal sup. R	21, 30, 48	3.32	<0.001, corrected
PD6 - VH6	frontal mid. R	33, 39, 9	3.64	<0.001, uncorrected
	cingulate ant. R	15, 33, 24	3.47	<0.001, uncorrected
	cingulate mid. L	-3, -15, 42	3.21	<0.001, uncorrected
	lingual L	-15, -84, 0	3.33	<0.001, corrected
	fusiform gyrus L	-33, -51, -3	2.99	<0.001, corrected
	fusiform gyrus R	36, -63, -18	2.65	<0.001, corrected

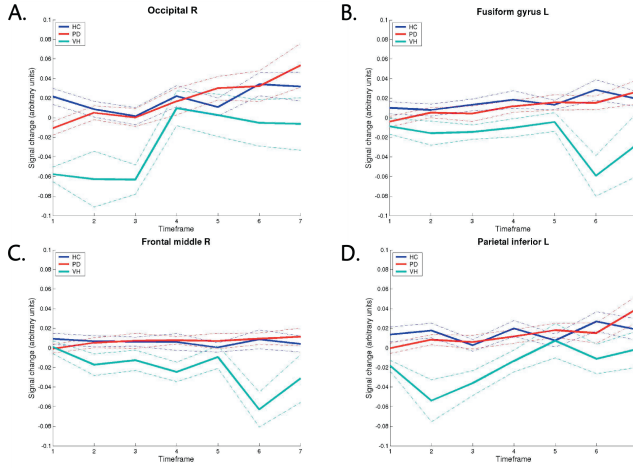
## C. Before pop-out: HC versus PDwithVH

Contrast:	Anatomical region	MNI-coordinates	T (voxel level)	p-value (cluster level)
HC2 - VH2	parietal inf. L	-45, -51, 39	3.10	<0.001, corrected
	occipital sup. L	18, -84, 18	2.69	<0.001, corrected
	occipital sup. R	21, -78, 27	2.34	<0.001, corrected
	occipital mid. R	33, -72, 24	2.29	<0.001, corrected
	occipital mid. L	-30, -78, 18	2.06	<0.001, corrected
HC6 - VH6	frontal mid. R	33, 42, 9	3.98	<0.001, corrected
	lingual gyrus L	-21, -57, 0	3.27	<0.001, corrected
	cingulate mid. L	-3, -12, 42	3.00	<0.001, corrected
	fusiform gyrus R	36, -63, -18	2.75	<0.001, corrected
	fusiform gyrus L	-30, -36, -18	2.71	<0.001, corrected

**Table 4.2:** A. All three groups showed robust activation of bilateral fusiform and lingual gyrus (at  $p < 0.001$ ,  $k = 20$ ). In the group comparisons, no differences between groups were observed at the moment of pop-out (data not shown). Before pop-out, differences were observed between PD and VH (B) and between HC and VH (C) in the time frames 2-6 (2=-5.8→-4.6 sec, 3=-4.6→-3.5 sec, 4=-3.5→-2.3 sec, 5=-2.3→-1.2 sec, 6=-1.2→pop-out) at  $p < 0.05$ ,  $k = 20$ . Relatively increased activation in PD, compared to VH (B) and also in HC, compared to VH (C) was seen (i.e. relatively decreased activation in VH, compared to both PD and HC). In 4.2B and 4.2C, statistical significance at cluster-level, after volume correction, may be influenced by the summed size of confluent clusters.



**Figure 4.3: Cerebral activation patterns before image recognition.** FIR results showing activations from 6.9 seconds before pop-out until pop-out of all groups separately at  $p < 0.01$  uncorrected,  $k=20$  (A), group comparisons between PDwithVH and PDnonVH at  $p < 0.05$  uncorrected,  $k=20$  (B) and group comparisons between PDwithVH and healthy controls at  $p < 0.05$  uncorrected,  $k=20$  (C).



**Figure 4.4: Time courses.** Plots showing the time courses with standard error of the mean (—) in healthy controls (HC), PDnonVH (PD) and PDwithVH (VH) from 6.9 sec before pop-out (−6.9 sec→−5.8 sec, time bin 1) until 1.15 sec after pop-out (pop-out→+1.15 sec, time bin 7)

longer than 30 seconds, and signal-to-noise consequently would have further increased, probably more patients would have been able to recognize the image, subsequently leading to a longer mean time until recognition [see also Meppelink et al. (2008)]. The time until image recognition was corrected for bradykinesia, by means of subtracting the mean reaction time per subject on the colour change from the recognition time. The fact that appropriate extrastriate visual areas were activated at pop-out in all three groups supported the adequacy of our strategy to define this event after correction for reaction time. Mean reaction times on the colour changing fixation square were similar in PDwithVH and PDnonVH, supporting our view that reduced activations were not explained by a generally reduced psycho-motor speed.

#### 4.5.2 Impaired extrastriate visual processing

By using FIR models, we were able to assess successive changes in the cerebral distribution of activations during the presentation of gradually revealed images. Just before and during pop-out, activation of occipito-temporal, inferior parietal and inferior prefrontal areas was seen in healthy controls. This is consistent with previous studies that have addressed visual perception and image recognition of gradually revealed images (James et al., 2000; Kleinschmidt

et al., 2002; Eger et al., 2006).

We showed that specifically PDwithVH, as compared to both PDnonVH and healthy controls, had reduced activation of the lateral occipital cortex several seconds before pop-out and reduced activation of the ventral temporal cortex just before pop-out. This might indicate a disturbance at a processing stage beyond V1 in which the normal brain uses scant information to predict the structure of features in an impoverished scenery (Summerfield and Koechlin, 2008). Indeed cortical regions at the lateral and ventral occipito-temporal junctions are important for visual object recognition (Malach et al., 1995; Grill-Spector, 2003). The fusiform gyrus, lateral occipital complex and middle temporal gyrus are involved in the visual perception of a range of both living and non-living objects, while the parahippocampal gyrus is predominantly involved in the perception of scenes (Malach et al., 1995; Downing et al., 2006). Therefore our finding provides support for our first hypothesis that bottom-up visual processing is impaired in PDwithVH. It is important to notice that this impaired visual processing was independent of visual acuity, which was equal in all groups, or contrast sensitivity, which was similar in PD patients with and without VH. To what extent other variables, like the angle of view of objects or colour discrimination are involved, could be a topic for future research.

Reduced activation of the lateral occipital cortex was already present from 5.8 seconds before pop-out in PDwithVH. Reduced activation of the inferior temporal cortex occurred just before pop-out in PDwithVH, while both occipital and temporal activation appeared to normalize (i.e. no differences between groups) when the image was fully perceived (see also figure 4.2). Following this early reduced activation of the lateral occipital cortex, significantly reduced activation before pop-out of frontal regions was seen, compared to PDnonVH, while a trend towards reduced frontal activation was seen when compared to healthy controls (data not shown). Just before pop-out, significantly decreased activation of the ventral temporal cortex was observed. Such a time-dependent defect underscores the importance to apply a dynamic paradigm in which images are gradually revealed, probably providing a more natural visual perceptual situation.

Clinical studies have shown impaired object perception in PD patients compared to healthy controls (Laatu et al., 2004; Barnes et al., 2003). More interestingly, several studies have shown that non-demented PDwithVH had more severely impaired object perception than PDnonVH (Barnes et al., 2003; Ramirez-Ruiz et al., 2006; Meppelink et al., 2008). Impaired processing within cortical visual pathways has further been inferred from functional imaging with IMP-SPECT and FDG-PET that have demonstrated baseline hypoperfusion or hypometabolism of temporal gyri (Boecker et al., 2007; Matsui et al., 2006a;

Okada et al., 1999; Oishi et al., 2005) and the occipital cortex (Matsui et al., 2006a; Nagano-Saito et al., 2004; Boecker et al., 2007) in PDwithVH, compared to PDnonVH. One of these studies reported hypoperfusion of the fusiform gyrus, together with hyperperfusion of the middle and superior temporal lobe (Oishi et al., 2005). Structural indicators for impaired visual cortex function in PD are further provided by MRI that has revealed atrophy of the (occipital) lingual gyrus in PDwithVH, compared to PDnonVH and healthy controls (Ramirez-Ruiz et al., 2007b). Future studies might investigate whether cortical atrophy is confined to the occipital lobe or if the temporal cortex is also affected. Finally, neuropathological examination has shown that a higher density of Lewy bodies in the temporal lobe was associated with VH in PD (Harding et al., 2002). These findings lead to the conclusion that impairment of the ventral and lateral extrastriate visual cortex in PD patients indicates a risk for the occurrence of VH.

Partial sensory deprivation is a long-appreciated risk factor for hallucinations in other clinical contexts like CBS. In CBS, complex VH occur in patients with acquired visual impairment without psychiatric disorders. The current view on its pathogenesis is that VH result from the release of visual cortical activity following the loss of visual inputs, also referred to as deafferentation (Burke, 2002). Relative impairment of visual processing in the occipito-temporal cortex in PDwithVH might thus predispose to the occurrence of VH via a “release” of higher order visual cortices within attentional and visual perceptual networks like the prefrontal cortex (Collerton et al., 2005).

### **4.5.3 Fronto-parietal visual processing**

Our second hypothesis was that reduced bottom-up visual cortical processing in PDwithVH might lead to an increased reliance on top-down visual processing, reflected by activation of the basal ganglia and/or prefrontal cortex (see e.g. Silbersweig et al. (1995)). No such increases of activation were observed, which implied that we did not gain arguments in favor of a compensatory role of these systems during visual processing in PDwithVH.

In contrast, in the period before image recognition decreased activation of the right superior frontal gyrus was seen in PDwithVH, compared to PDnonVH, and decreased activation of the middle frontal gyrus was seen in PDwithVH compared to both PDnonVH and healthy controls. In addition, a decreased activation of the inferior parietal cortex was seen in PDwithVH, compared to healthy controls only. The ventral prefrontal- and inferior parietal regions have

been implicated in previous studies that investigated visual perception of gradually revealed images in healthy controls and seem to play an important role in the integration of sensory and mnemonic information. Like in our healthy control group, visual awareness (i.e. perception) in these studies activated a network of ventral visual cortex, inferior frontal gyrus and lateral/inferior parietal cortex (Kleinschmidt et al., 2002; Eger et al., 2006). These parietal and prefrontal cortex activations were interpreted as involvement of higher order areas in top-down facilitation of image recognition (Eger et al., 2006). So it seems that, apart from impaired bottom-up visual processing before image recognition, a broader network including especially frontal cortical areas involved in top-down processing is impaired as well in PDwithVH.

A recent fMRI study has also shown reduced activation of the right ventro-lateral prefrontal cortex during face perception in cognitively impaired PDwithVH, compared to both PDnonVH and healthy controls (Ramirez-Ruiz et al., 2008). Dysfunction of the lateral prefrontal cortex was proposed to reflect a deficit in suppression of irrelevant stimuli, which might predispose to VH (Ramirez-Ruiz et al., 2008). Another implication of the reduced activation of ventro-lateral prefrontal cortex in PDwithVH is that these patients may have reduced tendency to address external stimuli. While lateral prefrontal regions are associated with externally cued behavior, medial prefrontal activation is associated with internally guided behavior (de Jong and Paans, 2007). The superior frontal gyrus plays a role in endogenous allocation and maintenance of visual attention and was shown to be involved in the inhibition of internally represented information (Corbetta et al., 2002; de Jong and Paans, 2007).

In the present study, frontal hypoactivation was only seen in the stage preceding image recognition and not when the image was fully perceived. In contrast, Ramirez-Ruiz et al. found relative frontal hypoactivation in PDwithVH during image perception (Ramirez-Ruiz et al., 2008). One might speculate that the preserved prefrontal activation during image recognition in the present study reflected the relative cognitive preserved patient sample in our study. Generally, it seems that non-demented PD patients with VH indeed have more impairments in executive functioning, when compared to PD patients without VH, who again are worse than healthy control subjects [for example Barnes and Boubert (2008)]. The influence of executive dysfunction is widespread and might therefore explain a considerable part of behavioral and imaging results. Even in PD patients with dementia, MMSE scores can be relatively spared, while scores on the FAB are decreased and thus seem to better reflect cognitive impairments in PD patients. Executive dysfunction might indeed be related to lower performance in perceptual tasks, making it unclear whether visual

perception itself is impaired or whether lower scores (or activations) reflect executive dysfunction. Our PD patient groups were matched on both cognition and executive functioning, making it less likely that the observed decreased activations before image recognition are directly associated with one of these factors. Possibly, results would have been even stronger when patients were not matched on executive functioning, but in that case conclusions regarding the perceptual problems in PDwithVH would have been less strong. Because a trend towards lower scores on executive functioning was seen in PDwithVH, the FIR analysis was repeated with FAB scores as a covariate, which had no effect on the results (data not shown).

Frontal regions might also be implicated in sustained attention (Johannsen et al., 1997), which was shown previously to be more impaired even in cognitively preserved PDwithVH, compared to PDnonVH, who again performed worse than healthy controls (Meppelink et al., 2008). Although we have corrected for attention, i.e. all subjects in all groups had adequate attention during performance of the task, this reduced activation of the middle frontal gyrus might still reflect subtle underlying attentional deficits in PDwithVH.

#### **4.5.4 VH in Parkinson's disease, proposed mechanism**

Because none of the participating subjects experienced VH during scanning, our pop-out movies are an indirect way to measure functional cerebral impairments associated with VH. While in the present study we showed that the ventral/lateral temporal cortex and part of the prefrontal cortex were relatively impaired in PDwithVH, one may still assume that activation increases occur in these regions during VH in these patients. It was shown before that perfusion of the inferior frontal gyrus was increased during VH of a spider in one PD patient, together with increased perfusion of visual association areas (Kataoka et al., 2008). A comparable cerebral activation pattern was seen during hallucinations in patients with schizophrenia. Auditory and visual association cortices showed increased perfusion during auditory or visual hallucinations, respectively. Additionally, increased perfusion of the orbitofrontal cortex and the striatum was seen during hallucinations in these patients with schizophrenia (Silbersweig et al., 1995).

It is unclear however, which cortical region initiates activation increases within the visual perceptual network of temporal, frontal and perhaps parietal cortical activation during VH. An intra-operative stimulation study in epilepsy patients showed that stimulation of the prefrontal cortex (inferior frontal gyrus) can evoke complex VH, probably by propagation of activity from the prefrontal

cortex along white matter tracts [uncinate fasciculus (Catani and Mesulam, 2008)] to the ventral occipito-temporal lobe (Blanke et al., 2000). Furthermore orbitofrontal seizures can present with complex VH, probably also by propagation of epileptic activity to temporal regions (La Vega-Talbot et al., 2006).

## 4.6 Conclusion

Increased vulnerability for VH in PD is associated with impaired visual object processing in ventral/lateral visual association cortices, providing support for our hypothesis of impaired bottom-up visual processing in PDwithVH. Moreover, reduced activation in a wider network including lateral prefrontal in PDwithVH suggested that early stages at which top-down information is given are additionally impaired. We did not find arguments for compensatory increases of activation in PDwithVH, and thus no support for a link between vulnerability for VH and increased reliance on top-down processing during visual perception.

## 4.7 Acknowledgements

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